REMARKS/ARGUMENTS

This is a response to the Office Action mailed December 23, 2003, in the above-identified application.

Applicant notes and appreciates the NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY mailed November 26, 2003, whereby the prosecution of this application is now being handled by the below-signed attorney, at the St. Louis, Missouri address of the Pharmacia Corporate Patent Department. Since said attorney is new to this application, he submits the following initial brief statement of his understanding of its prosecution to date in order to reduce the issues and facilitate further prosecution.

Prosecution to Date

This application was originally filed with Claims 1-149.

A first Office Action on the merits was mailed November 11, 2000, Paper No. 6. A response to that Office Action was filed on April 23, 2001 as AMENDMENT A.

A further Office Action was mailed September 13, 2001 with no action on the merits but with a Restriction Requirement with three groups designated as follows:

Group I Claims 1-75, drawn to methods of antiviral treatment
Group II Claims 76-147, drawn to pharmaceutical compositions
Group III Claims 148-149, drawn to methods of synthesis of compositions

A response to the Restriction Requirement was filed on October 15, 2001, which included a provisional election of the Group I Claims 1-75.

A duplicate copy of said response of October 15, 2001 was forwarded to the PTO by Facsimile on May 5, 2003, in view of a telephone conversation on May 2, 2003 between the Examiner and the previous attorney of record.

An additional duplicate copy of said response of October 15, 2001 was forwarded to the PTO by Facsimile on August 7, 2003.

An Office Action was mailed September 29, 2003 with a one-month or 30-day shortened response date which indicated that the reply filed on "August 25, 2003" (understood to mean the August 7, 2003 reply by Facsimile) was not fully responsive to the prior Office Action, since there was no election of a species as required on page 3 of the Restriction Requirement.

A response to the September 29, 2003 Office Action was filed October 29, 2003, which included an election of species to a method of treating a hepatitis virus infection in a mammal comprising administering to said mammal N-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol. Claims 1-3, 7-11, 15-19, 23-27, 31-35, 39-42, 46-51, 55-62, 66-71, and 75 were said to read on the elected species. [As noted by the Examiner, claims after the first claim 42 were incorrectly numbered since there were two claims numbered 42].

Present Office Action

An Office Action on the merits was mailed December 23, 2003. Applicant's election of the Group I, claims 1-75 (renumbered 1-76), and the further election of the aforesaid species, were acknowledged and treated as an election without traverse.

It was stated that there were two claims with the number 42, wherefore the second 42 and all remaining claims were each newly renumbered one number higher by the Examiner. Applicant regrets and apologizes for this mistake in numbering. In the aforesaid Listing of Claims, the original erroneously numbered claims are renumbered.

The Examiner has withdrawn from further consideration those claims "drawn to non-elected Groups". It is noted that the withdrawn method of treatment claims are directed specifically to species in which W, X, Y, and Z are each defined as "alkanoyl". That is, those compounds in which all of the free hydroxyls on the ring are O-acylated.

As stated above, it is the intention of the below-signed attorney to reduce the issues in this case and facilitate the further prosecution. Therefore, it is desired to first give attention to two matters which it is believed can be readily removed from issue: the matter of double patenting and the matter of claims that may appear to be prolix or substantially redundant.

Double Patenting

All of the claims remaining in the case have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of co-pending Application No. 09/355,446. Said co-pending application has now been allowed and issued February 10, 2004 as U.S. Patent No. 6,689,759. Said co-pending application was allowed with claims 1-34 and 70-90, all of which relate to the method of treatment with a combination therapy. In the claimed combination therapy in said co-pending application, the N-substituted-DNJ type compounds are combined with nucleosides and/or nucleotides.

In order to overcome the double patenting rejection, all of the method-of-treatment claims which recite said combination therapy with nucleosides and/or nucleotides are herewith cancelled, i.e., claims 41-58 (renumbered by the Examiner as 42-59).

Claims 59-67 (renumbered by the Examiner as claims 60-68) are "substantially exclusive of" administration of antiviral compounds such as nucleosides or nucleotides, and claims 68-76 (renumbered as claims 69-77) are "substantially exclusive of" administration of antiviral compounds other than compounds of Formula I.

It is thus respectfully submitted that Claims 59-76 (renumbered 60-77) do not involve double patenting with said co-pending Application No. 09/355,446, which specifically requires combination therapy that includes an anti-hepatitis virus effective amount of nucleotide or nucleoside. Therefore, applicant requests withdrawal of the double patenting rejection as to claims 59-77 (renumbered 60-77). Nevertheless, applicant offers to submit a terminal disclaimer in the event the Examiner maintains the double patenting rejection with respect to said claims or other claims remaining in the case. The conflicting application is commonly owned with this application.

Potentially Prolix Claims

In order to facilitate the further prosecution of this case, applicant wishes to reduce the number of claims at issue by canceling claims that potentially may be deemed prolix. It is noted that the originally filed method-of-use claims included five sets of eight claims in each set for a total of 40 claims (claims 1-40). In these five sets of claims, claims 1, 9, 17, 25 and 33 are generic, and each generic claim is followed with seven dependent claims. In order to reduce the number of claims in issue, applicant herewith retains one of these sets of claims and cancels the remaining four sets of claims without prejudice. Accordingly, of the first 40 claims, generic claim 25 and claims dependent thereon are retained, and generic claims 1, 9, 17, and 33 and claims dependent thereon are cancelled without prejudice.

Claims 41-58 (renumbered as claims 41-59), which claim combination therapy, are cancelled.

Claims 76-149 (renumbered as claims 77-150), which are the non-elected Group II and III claims, are cancelled without prejudice to their re-filing as divisional/continuation claims pursuant to 35 USC §§ 120-121.

Claims 151-153 are three new claims dependent on retained Claim 25. Claim 151 recites a "more preferably" C_8 to C_{12} alkyl chain length of R in the Formula I compounds as specifically disclosed in the last line of page 12 of the specification. Claims 152-153 recite two compounds specifically illustrated in Example 3, Table 2, at pages 40-41 of the specification.

Claims Rejections – 35 USC § 103

The Examiner's presumption that the subject matter of the various claims remaining in this application were commonly owned at the time any inventions covered therein were made is correct.

Claims 1-3, 7-11, 14-19, 23-27, 31-35, 39-40, 59-63, 67-77, 76 and 77 have been rejected under 35 U.S.C. 103(a) as being unpatentable over *Block et al.* (WO 95/19172) in view of Partis et al. (U.S. Patent 5,303,638). This rejection is traversed for reasons as follows:

It is understood by applicant that in this rejection the claims are each renumbered one higher, starting with the original second claim 42.

It is noted that in this rejection claims 76 and 77 are included in the group designated claims 67-77 and again separately as claims 76 and 77. It is also noted that the group designated claims 67-77 includes claims 73-75 (originally numbered 72-74), which were withdrawn by the Examiner as drawn to no elected Groups. Therefore, the below-signed attorney believes and understands that by the group designated "67-77" the Examiner actually meat "67-72".

In view of the foregoing understanding and the cancellation of claims herewith as set forth in the Listing of Claims, the rejection is now moot as to claims 1-3, 7-11, 15-19, 23 and 24, 31-35, 39-40, 67, 68, 76 and 77. Therefore, as presently understood, the rejection now applies only to the claims designated as 25-27, 60-63, and 69-72, which remain in this case.

Argument re *Partis et al.* Teachings

Claims 25, 60 and 63 are generic. Each of these three generic claims is amended herewith whereby the term "antiviral" is amended to the term "anti-hepatitis virus" effective amount of the N-substituted DNJ type compound or salt thereof. All the claims in this application

thereby are clearly directed to treatment of **hepatitis virus** as distinguished from treatment of other viruses such as the **retrovirus** or the **human immunodeficiency virus (HIV)** or **lentivirus** as taught by the *Partis et al.* reference.

There are significant differences between hepatitis virus to which the method of the present invention is directed, and retroviruses such as HIV or lentivirus with which the *Partis et al.* reference is concerned. First of all, retroviruses are **RNA tumor viruses**, whereas hepatitis viruses are **DNA** viruses in which RNA is transcribed into DNA.

Attached hereto is a copy of pages 29 and 35 from the scientific treatise on *Virology* by Wolfgang K. Jolik, Third Edition, 1988, Appleton & Lange, that describes essential differences between: (A) the hepadnaviruses which include hepatitis B virus, and (B) the retroviruses which include lentivirus and HIV. The hepatitis virus is a completely different **Family** of virus than the lentivirus and HIV of *Partis et al.* Hepatitis virus is not simply a different sub-Family, Genus or Species of the lentivirus and HIV. Thus, it is not obvious to the person skilled in the art that inhibition of a virus in the Family described by *Partis et al.* would allow prediction of activity against a different Family of virus such as the hepatitis virus as claimed herein.

The *Jolik* scientific treatise also makes particular note of the Woodchuck hepatitis B virus as representative of the hepadnaviruses. Examples 5 and 6 at pages 43-49 in the present specification clearly demonstrate the effective anti-hepatitis virus activity of the claimed method of the invention with the Woodchuck hepatitis B virus model. It is respectfully submitted that there is nothing whatsoever in *Partis et al.* which even remotely suggests treatment of hepatitis virus as demonstrated and claimed in the present application.

Argument re *Block et al.* Teachings

The *Block et al.* reference discloses the method for the treatment of hepatitis B virus with N-alkyl derivatives of 1,5-dideoxy-1,5-imino-D-glucitol in which the alkyl contains from 3 to 6

carbon atoms. In the only disclosed experimental data in the reference the alkyl group is the 4-carbon butyl group. There is no teaching or suggestion in the *Block et al.* reference that analogous compounds having 7 to 20 carbon atoms in the alkyl chain would have effective activity against hepatitis virus.

On the one hand, the alkyl chain having 3 to 6 carbon atoms as taught by *Block et al.* is by definition a relatively **short** chain. On the other hand, the alkyl chain having 7 to 20 carbon atoms as in the present claims is a relatively **long** chain. In the field of pharmaceutical compounds, it is not reasonable to draw an analogy from an active compound having a short chain substituent to an active compound having a long chain substituent. In the *Block et al.* reference, anti-hepatitis virus activity was demonstrated only with the analog in which the alkyl group was "butyl".

In accordance with the present invention it was found that the **long** chain analog as illustrated by the N-nonyl derivative was substantially more active than the **short** chain analog illustrated by the N-butyl derivative. For example, as illustrated in Table 3, pages 41-42, a concentration of 0.5 – 1.0 μg/ml of N-nonyl DNJ gave a 90% inhibition of hepatitis B virus secretion, whereas even at a substantially higher concentration of 200 μg/ml, no inhibition was seen with an N-butyl analog of DNJ. The ratio of activity of the nonyl vs. the butyl compound thus is >2000:1. Although the N-butyl analog was the 3,4-diacetate, these four additional alkyl carbons are not believed to have materially affected the results. If anything, they would make the total number of alkyl carbons more close to that of the N-nonyl analog. In summary, there was no expectation from *Block et al.* of such an advantage of inhibition with the longer chain N-nonyl derivative compared to the N-butyl analog. If anything, the expectation was that inhibition would reach a maximum at the C_4 chain length and taper off up the C_6 chain length, which is the maximum chain length in the C_3-C_6 range taught by *Block et al.*

Incidentally, the below-signed attorney filed and prosecuted the *Block et al.* application and can assure the Examiner that there was no belief or expectation by the inventors that the active anti-hepatitis virus activity demonstrated with the short chain "butyl" derivative would be

extendable to long chain alkyl derivatives having 7 to 20 carbon atoms in the alkyl group. One of the co-inventors in *Block et al.* is Baruch S. Blumberg, who is the world's leading scientist in the field of hepatitis B virus and the winner of the 1976 Nobel Prize in Medicine for his work on that virus. It is respectfully submitted that the fact that his patent does not suggest anti-hepatitis virus activity with analogous compounds having more than 6 carbon atoms in the alkyl group is indicative that extension of the chain length from the demonstrated "butyl" to beyond 6 carbon atoms for treatment of hepatitis virus was neither reasonable nor expected. That is, although *Block et al.* suggest modification of the alkyl chain from the demonstrated 4 carbon analog, the suggested modification is only up to 6 carbon atoms.

Argument re *Partis et al.* + *Block et al.* Teachings

In the present Office Action it is concluded that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the 3 to 6 carbon chain length of the alkyl DNJ compound used to treat hepatitis virus of *Block et al.*, by increasing the number of carbons in the chain to 9 since *Partis et al.* teach that the pharmacokinetics of nonyl-DNJ were superior to butyl-DNJ. This conclusion is refuted, first of all, because as has been noted above, the *Block* co-inventor Blumberg is an expert in the field of the invention and yet did not suggest to modify the butyl to more than 6 carbons for treatment of hepatitis virus infection

Secondly, although as alleged by the Examiner at pages 5-6 of the Office Action, the *Partis et al.* reference teaches that the pharmacokinetics of nonyl-NJ were superior to butyl-DNJ, this alleged superiority can reasonably be interpreted as advanced only for the disclosed use for the treatment of retroviruses such as lentivirus and HIV. There is nothing in the *Partis et al.* teaching that the nonyl-DNJ would have effective anti-hepatitis virus activity, let alone superior anti-hepatitis virus activity over that obtained with the butyl-DNJ. The only effective antiviral activity taught by *Partis et al.* is activity against retroviruses such as lentivirus and HIV. The present invention relates to effective treatment of hepatitis virus, not effective treatment of lentivirus or HIV, which is in a different Family of viruses.

The claimed invention is not directed to the pharmacokinetics of the N-alkyl DNJ compounds as taught by *Partis et al.*, but to their anti-hepatitis virus activity. The serum level pharmacokinetics of N-nonyl-DNJ as compared to that of N-butyl-DNJ is not an obvious requirement for the treatment of hepatitis virus. In fact, inhibition of HIV virus as taught by *Partis et al.* requires drug distribution into the blood stream wherein reside the drug target carrier white cells, e.g., lymphocytes, that are major HIV virus reproductive cells. In sharp contrast, inhibition of hepatitis virus *in vivo* requires that the inhibitor be distributed out of the blood stream into the liver. Again, it is not obvious that compounds that inhibit HIV in circulating white cells would inhibit hepatitis virus cell in the liver.

By way of further comparison over the prior art, in the experimental results shown in the present application in Tables 2 and 3 of Example 3, at pages 39-42, as discussed above, it is seen that the "nonyl" analog provided substantially greater anti-hepatitis virus activity than the "butyl" analog, by a ratio of >2000:1. There is nothing in *Block et al.* and *Partis et al.* to suggest such substantial difference in results. It is respectfully submitted that the experimental data in said Example 3, when taken together with the foregoing arguments, effectively overcomes the *prima facie* obviousness rejection under 35 U.S.C. 103(a).

Rejection re Combination with *Schinazi* is Moot

Claims 41-43, 47-52, and 56-58 have been rejected under 35 U.S.C. 103(a) as being unpatentable over *Block et al.* in view of *Partis et al.* as applied to the claims in the foregoing rejection and further in view of *Schinazi et al.* (U.S. Patent 5,444,063). It is respectfully submitted that this rejection is now moot in view of the cancellation of Claims 41-43, 47-52, and 56-58.

Request for Allowance of Claims 25-27, 60-63, 69-72, and 151-153

In view of the above amendment and remarks, it is respectfully submitted that Claims 25-27, 60-63, 69-72, and 151-153 are allowable. Allowance thereof is courteously solicited.

Respectfully submitted,

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SJM/mrr

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